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The Dose-Response Relationship of Ondansetron in Preventing Postoperative Emesis in Pediatric Patients Undergoing Ambulatory Surgery

Mehernoor F. Watcha, M.D., Paul J. Bras, M.B., B.S., F.R.C.A.,† Gary D. Cieslak, M.D.,‡ John H. Pennant, M.A., M.B., B.S., F.R.C.A.§*

Background: **Postoperative nausea and vomiting is a distressing anesthetic complication that may delay discharge after ambulatory surgery. Effective prophylaxis for postoperative nausea and vomiting can be achieved in adults with lower doses of ondansetron, a 5-hydroxytryptamine subtype 3 receptor antagonist, compared with chemotherapy-induced emesis. However, the doses of ondansetron used in preventing postoperative nausea and vomiting in children are based on data from chemotherapy-induced emesis. The dose-related efficacy of intravenous ondansetron in the prophylaxis of postoperative emesis in the pediatric outpatient population was determined.**

Methods: **In a double-blind, randomized placebo-controlled study, 130 patients (mean age 5.7 ± 3.4 yr) received placebo, 10, 50, or 100 μg/kg ondansetron during a standardized anesthetic. Episodes of postoperative vomiting or retching were recorded.**

Results: **Intravenous ondansetron in a dose of 50 μg/kg was more effective than placebo or a dose of 10 μg/kg in controlling the incidence and frequency of emesis in the hospital and during the first 24 postoperative hours. Increasing the dose of ondansetron to 100 μg/kg intravenously did not significantly reduce the incidence or frequency of emesis compared to 50 μg/kg intravenously.**

Conclusions: **Intravenous ondansetron in a dose of 50 μg/kg is as effective as larger doses for the prophylaxis of emesis in children undergoing surgical procedures known to be associated with an increased risk for postoperative nausea and vomiting. (Key words: Anesthesia: ambulatory; pediatrics. Antiemetics: ondansetron. Complications: postoperative vomiting.)**

* Associate Professor; Director of Pediatric Research.

† Clinical Fellow, Pediatric Anesthesia.

‡ Clinical Instructor.

§ Assistant Professor.

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Address reprint requests to Dr. Watcha: Department of Anesthesiology and Pain Management, University of Texas, Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235-9068.

POSTOPERATIVE nausea and vomiting not only causes distress to the patient, tension on sutures, and potential bleeding at the operative site, but also may lead to delayed discharge from the ambulatory surgical center, fluid and electrolyte imbalance, and unanticipated hospital admission.[1] Ondansetron, a selective antagonist of the 5-hydroxytryptamine subtype 3 receptor, is highly effective in reducing the incidence of chemotherapy-induced and postoperative nausea and vomiting (PONV).[2,3] The doses first used for the prophylactic management of PONV in children (100–150 μg/kg) were based on data from treatment of chemotherapy-induced emesis.[4–8] However, effective antiemetic prophylaxis can be achieved with smaller doses for PONV than for chemotherapy-induced emesis in adults.[9–11] There are no data available on the dose-related efficacy of ondansetron when used as the sole antiemetic agent for the prevention of PONV in children. In this double-blind, placebo-controlled study, we determined the dose-response relationship of ondansetron in the prophylaxis of PONV in children.

Materials and Methods

With Institutional Review Board approval and parental written informed consent, we studied 130 healthy ASA physical status 1–2 children (mean age 5.7 yr, range 1.5–15 yr) scheduled to receive general endotracheal anesthesia for outpatient surgical procedures known to be associated with increased PONV (*e.g.*, strabismus correction, tonsillo-adenoidectomy or dental procedures).[1,12–14] We excluded patients who had experienced vomiting or retching or who received drugs known to have antiemetic effects (*e.g.*, tricyclic

antidepressants, scopolamine, phenothiazines, lorazepam, corticosteroids, trimethobenzamides) in the 24 h before surgery. We also excluded children with a history of allergy or other contraindication to the use of inhalational, neuromuscular blocking, or antiserotonin agents.

After a minimum fast of 3 h (for clear liquids), all children received 0.5 mg/kg oral midazolam 15–30 min before induction with halothane and nitrous oxide in oxygen *via* a face mask. The child's behavior during induction was assessed on a four-point scale (1 = asleep, 2 = calm, 3 = anxious, crying but can be comforted, and 4 = very anxious, uncontrollable). After induction of anesthesia and the establishment of venous access, tracheal intubation was facilitated with 0.1 mg/kg intravenous vecuronium and anesthesia maintained with isoflurane and nitrous oxide, along with 2 μg/kg intravenous fentanyl. The concentration of isoflurane was adjusted to maintain blood pressure and heart rate within 15% of baseline values. In addition, patients were randomly assigned on the basis of a computer-generated number to receive placebo or ondansetron in a dose of 10, 50, or 100 μg/kg (maximum 4 mg) before the surgical incision. All study drugs were diluted by a pharmacist to a fixed volume of 2 ml to maintain the double-blind nature of the study and were administered intravenously over 30 s. At the end of the surgical procedure, residual neuromuscular blockade was antagonized in all patients with 0.05–0.07 mg/kg neostigmine and 0.01–0.02 mg/kg glycopyrrolate, the stomach was suctioned, and the trachea was extubated when the patient was awake. We recorded all measures taken to maintain a patent airway after tracheal extubation.

In the postanesthesia care unit, pain was assessed by an objective pain score as described by Hannallah *et al.*[15] Patients in severe pain (objective pain scores > 6) received 1–2 μg/kg intravenous fentanyl, whereas milder pain (scores of 3–5) was managed with oral acetaminophen (10 mg/kg) with codeine (1 mg/kg). Oral intake was permitted but not required before discharge. However, adequate intravenous fluids were administered to correct preoperative deficits and intraoperative blood loss and to provide for the normal maintenance requirements.

During the preoperative interview, we inquired about any history of motion sickness, gastroesophageal reflux, or PONV. We recorded the behavior during induction using the four-point scale mentioned above. We also recorded the type and duration of surgery and anesthesia, all medications and intravenous fluids administered during the perioperative period, along with the times from the end of surgery to eye opening, response to commands, first oral intake, ambulation, and discharge readiness from phase 1 and phase 2 recovery areas. Discharge criteria included a fully awake child who recognized the parents, had stable vital signs (including oxyhemoglobin saturation > 95% in room air), and was free from persistent pain and emesis.

Vomiting was defined as the forceful expulsion of gastric contents from the mouth, whereas retching was defined as labored, spasmodic, rhythmic contractions of the respiratory muscles without the expulsion of gastric contents. Nausea, a subjective feeling of the urge to vomit, was not evaluated in the study because of the young age of the patients. Episodes of vomiting or retching had to be separated by 1 min before being considered distinct episodes. Patients who had two or more episodes of emesis (vomiting or retching) while in the hospital received 0.1–0.15 mg/kg intravenous metoclopramide as rescue antiemetic therapy. The protocol permitted the use of other antiemetics, such as droperidol, trimethobenzamide, or promethazine at the discretion of the anesthesiologist if metoclopramide did not control emesis.

We recorded all emetic episodes in the postoperative period in the hospital. Interviews conducted *via* the telephone determined the postdischarge incidence of emesis, the time when the child's appetite and behavior returned to normal, and when the child's primary caretaker could return to a normal routine of household chores without having to concentrate on comforting and taking care of the child's postoperative problems. Finally, the caretaker was asked to assess the child's enjoyment of the first solid meal after the operation and to give a global assessment of the entire perioperative experience using a ten-point scale (from 0 = poor to 10 = excellent).

Statistical Methods

Power analysis determined that 28 patients were required in each group to have an 80% chance of detecting a 40% reduction in emesis at the 0.05 significance level. Analysis of variance was used to compare the age, weight, duration of surgery, anesthesia, and times from the end of surgery to tracheal extubation, arrival in the recovery area, eye opening, response to commands, and time to discharge, and the parental assessment of the global perioperative experience. Intergroup comparisons were made with Scheffé's test.

The patient's gender, history of motion sickness, PONV, type of surgical procedure, incidence of emesis during the hospital stay and during the first 24 h, and the number of patients requiring rescue antiemetic therapy were compared by Fisher's exact and chi-square tests with a Yates' continuity correction, as appropriate. The Mantel-Haenszel test was used to compare each of the ondansetron groups to the placebo group with regard to the number of patients free from emesis while in the hospital and during the entire 24-h period. For purposes of statistical analysis, patients were divided into subgroups based on the frequency of emesis over the first 24 postoperative hours. A contingency table was used to compare the number of patients with zero or one, two, and three or more episodes of emesis between the four study groups. All tests were two-tailed with P values < 0.05 being considered significant. Data are presented as mean ± SD unless otherwise stated.

Results

There were no significant differences between the four groups in patient age, gender, weight, ASA physical status, behavioral scores during induction, type and duration of surgical procedure, or history of motion sickness, gastroesophageal reflux, or PONV (table 1). In patients who underwent eye muscle surgery for the correction of strabismus, there were no significant differences between the groups in the number of muscles operated, patients who underwent operations involving the inferior oblique muscle, or patients who had repeat operations.[14] There also were no differences between the groups in the duration of anesthesia or in the time from the end of surgery to eye opening, ambulation, or response to commands or in the postoperative analgesic requirements.

There were no significant differences in the incidence of emesis between the placebo and 10-μg/kg groups and between the 50- and 100-μg/kg groups (table 2). The incidence of emesis while the patient was still in the hospital and the need for rescue antiemetic therapy were greater in the groups that received placebo compared to those receiving 50 or 100 μg/kg ondansetron. Similarly, the incidence of emesis over the entire 24-h period was greater in the placebo and 10-μg/kg groups compared to the 50- and 100-μg/kg groups, respectively (table 2). In addition, the number of patients with two or more emetic episodes was significantly larger in the placebo and 10-μg/kg groups compared to the 50- or 100-μg/kg groups (table 2).

Eighty-six percent of patients who received a single prophylactic intravenous ondansetron dose of 50 or 100 μg/kg remained free of emetic episodes during the entire 24-h period compared to only 45% of those receiving placebo or 10 μg/kg ondansetron ($P < 0.05$). All patients who required rescue antiemetic therapy with metoclopramide while in the hospital initially received placebo or 10 μg/kg ondansetron. These children had no further emetic episodes and required no

Table 1. Demographic Data

	Placebo	Odansetron		
		10 μg · kg^{-1}	50 μg · kg^{-1}	100 μg · kg^{-1}
Number (n)	33	32	32	33
Age (yr)	6.4 ± 4.1	5.7 ± 3.1	5.0 ± 2.7	5.7 ± 3.6
Gender M/F	14/19	15/17	17/15	17/16
ASA Physical Status 1/2	24/9	29/3	25/7	22/11
Weight (kg)	24.1 ± 15.6	23.7 ± 13.7	23.2 ± 14.1	24.1 ± 15.7
Operation				
Tonsilloadenoidectomy	10	9	7	8
Strabismus correction	15	16	14	15
Dental rehabilitation	4	5	9	7
Other eye and ENT cases*	4	2	2	3
Duration of surgery (min)	43 ± 38	38 ± 19	41 ± 25	43 ± 32
Duration of anesthesia (min)	74 ± 51	63 ± 20	65 ± 24	69 ± 33
PACU arrival (min)	12 ± 6	12 ± 5	11 ± 5	10 ± 4
Spontaneous eye opening (min)	24 ± 15	25 ± 15	22 ± 14	30 ± 20
Response to commands (min)	29 ± 17	29 ± 16	25 ± 15	34 ± 20

* Includes myringoplasties, tympanomastoidectomy, dacryocystorhinostomy, and palatoplasty.

Table 2. Emesis Related Data and Time from the End of Surgery to Discharge Readiness

		Odansetron		
	Placebo	10 $\mu g \cdot kg^{-1}$	50 $\mu g \cdot kg^{-1}$	100 $\mu g \cdot kg^{-1}$
Number	33	32	32	33
Incidence of predischarge emesis (%)	42	22	9*	9*
Required rescue antiemetic drugs (%)	24	9	0*	0*
Postdischarge emesis (%)	33	44†	12	9
Emesis during 0–24 h postoperation (%)	58	53†	19*	15*
Emetic frequency over 0–24 postoperation (%)				
0–1 vomit/24 h‡	43	48†	91*	88*
2 episodes/24 h	40	36	9	12
≥3 episodes/24 h	17	16	0	0
Parental assessment scores (mean ± SD)				
Patient with emesis	6.8 ± 1.7	6.3 ± 1.7	6.4 ± 1.1	7.0 ± 0.1
Patient free from emesis	7.4 ± 1.4	7.9 ± 1.3	7.2 ± 1.7	8.1 ± 1.3
Discharge readiness (min) (mean ± SD)	145 ± 49	125 ± 31	112 ± 33*	120 ± 37
Side effects (%)				
Headache	9	13	9	6
Constipation	3	0	0	0
Drowsiness	12	6	3	6

* $P < 0.05$ *versus* placebo group.

† $P < 0.05$ *versus* 50 and 100 $\mu g \cdot kg^{-1}$ group.

‡ Patients free from emesis are included in this group but not in the preceding rows (predischarge emesis, need for rescue antiemetics, postdischarge, and 24-h emesis).

other antiemetic therapy before discharge. However, 78% of patients who received metoclopramide rescue therapy in the hospital vomited at least once after discharge. One of these patients (who had received 10 μg/kg ondansetron) required readmission to the hospital for the management of persistent emesis.

Vomiting while in the hospital was associated with a statistically significant 37-min increase in the mean time to discharge (table 3). The parental assessment of the global perioperative experience correlated with the occurrence and frequency of emesis, with significantly lower scores assigned in the patients who vomited more often (table 3).

There were no significant differences between the four groups in the number of patients who complained of headache, constipation, or excessive drowsiness after discharge from the hospital.

Discussion

This study showed that 50 μg/kg intravenous ondansetron provided more effective antiemetic prophylaxis than 10 μg/kg, but increasing the dose to 100 μg/kg did not improve the efficacy or further reduce the severity of postoperative emesis. In contrast, an intravenous dose of 10 μg/kg was not significantly different than placebo in preventing postoperative emesis. The incidence of emesis in our placebo and 100-μg/kg group are in keeping with previously published studies.[6,8,14,16,17] Similar results were noted in adult dose-ranging studies in which an intravenous dose of 4 mg was as effective as an 8-mg dose, and both were more effective than 1 mg or placebo in the control of nausea and vomiting. When efficacy in these studies was de-

Table 3. Emesis and Parental Assessment Scores of the Global Perioperative Experience

Group		*P* Value
Discharge time in patients with:		
In-hospital emesis	151 ± 49 min	
No predischarge emesis	114 ± 34 min	<0.01
Parental assessment scores in:		
Patients with any emesis during 0–24 h	6.6 ± 1.5	
Emesis-free patients	7.7 ± 1.5	<0.05
Parental assessment scores in patients with:		
0–1 episodes emesis/24 h	7.7 ± 1.5	
2 episodes emesis/24 h	6.8 ± 1.5	
≥3 episodes emesis/24 h	5.7 ± 1.6	<0.01

Values are mean ± SD, unless otherwise stated.

fined as emesis rather than nausea and/or vomiting, doses of 1, 4, and 8 mg were all better than placebo.[3,11,18,19] Because it was difficult to evaluate the subjective phenomenon of nausea in children, the endpoint in our study was limited to emesis. For the standard hypothetical 70-kg adult, doses of 1, 4, and 8 mg would equate to 14, 57, and 114 μg/kg, respectively.

Studies of blood levels after intravenous administration of ondansetron in healthy children during anesthesia have shown that a theoretical intravenous dose of 50 μg/kg ondansetron in a child will provide a similar area under the plasma concentration-time curve as a dose of 4 mg in adults.[20–22,‖] Although there are data on the pharmacodynamics of ondansetron in adults that suggest a relationship exists between the control of chemotherapy-induced emesis and the area under the plasma concentration-time curve,[22] no similar data are available in children for postoperative emesis. The large variability in kinetic data from different institutions makes it difficult to compare relationships between plasma concentration and effect in different age groups.

We noted that ondansetron in a single intravenous dose of 50 μg/kg was effective in achieving complete control of emesis over the entire 24-h study period in 81% of children. Similarly, Grunwald *et al.* have shown that a prophylactic dose of droperidol has an extended clinical antiemetic action in children.[23] In contrast to the efficacy of these agents in the prophylaxis of PONV, the use of metoclopramide as a rescue antiemetic was associated with only brief success in our study, with many patients vomiting again after discharge. These data suggest that single doses of metoclopramide are inadequate for full control of established postoperative emesis. Although ondansetron is effective in the therapy of PONV in adults, data on the optimal dose and frequency of administration of this agent for the satisfactory control of established postoperative emesis in the pediatric population were not available at the start of this study. There are also no available data on the dose of ondansetron required in children with a history of PONV. In adult studies, it has been suggested that higher doses of ondansetron may be required in patients who have a history of PONV.[18,19] Because the number of patients with a history of PONV was not large enough in our study to permit meaningful statistical analysis as a separate group, we are uncertain whether this pediatric subpopulation would benefit from the larger dose.

This study may be criticized for recruiting patients undergoing different operative procedures and for using a maximum dose of 4 mg ondansetron. As there were no significant differences in the distribution of operative procedures between the study groups, we believe it is unlikely that different conclusions would have been reached if the study were limited to one operation. The choice of the adult dose (4 mg ondansetron) as the upper limit in children is in keeping with standard anesthetic practices with other drugs, such as antibiotics and anticholinesterases. The use of an upper limit of 4 mg ondansetron resulted in a mean dose of 96 μg/kg in the high-dose ondansetron group, as five patients in this group received less than 100 μg/kg. There were no significant differences in the incidence of emesis in patients who received the full 100-μg/kg dose compared to the subgroup that received the maximum dose of 4 mg (2/5 *vs.* 4/28, $P > 0.05$). In addition, the conclusions regarding the lack of significant differences in the incidence of emesis between the groups receiving 50 and 100 μg/kg ondansetron were not altered by the deletion of the patients who received less than 100 μg/kg from this group in the statistical analysis.

In our study, we noted that ondansetron did not delay recovery from anesthesia as demonstrated by similar times from the end of surgery to arrival in the postanesthesia care unit, eye opening, and response to commands in patients who did or did not receive ondansetron (table 1). In keeping with previous reports, we noted a lack of major side effects, such as extrapyramidal reactions.[5,18,19] It has been suggested that this lack of major side effects with ondansetron permits the safe administration of larger doses to children at increased risk for postoperative emesis. This approach may be acceptable if the costs of ondansetron were in keeping with the costs of other antiemetic drugs. However, the acquisition price for this new drug is currently more than ten times as great as the costs for other drugs, such as droperidol and metoclopramide, if multidose vials are used, and even greater if single-dose vials are used and the residue is discarded. Earlier studies on ondansetron had used doses of 100 μg/kg, and our findings that doses of 50 μg/kg are just as effective as 100 μg/kg have obvious implications on the cost efficacy of this agent.

Our study was not designed to determine whether doses between 10 and 50 μg/kg are as effective as 50

‖ Blumer JL, Shurin S, Patrick S: Evaluation of pharmacokinetics, safety and efficacy of ondansetron in children receiving chemotherapy (abstract). Proc Am Soc Clin Oncol 9:332, 1990.

μg/kg for the prophylaxis of PONV, but future studies should be performed to provide such data. Additional studies are required to compare the relative costs and effectiveness of the prophylactic and therapeutic use of ondansetron with other antiemetics (droperidol, prochlorperazine, trimethobenzamides) in the pediatric population at both a high and a low risk for PONV. In these studies, the cost-effectiveness analyses should not be limited to the acquisition costs of the drugs but also should include the costs of managing side effects, such as extrapyramidal reactions, along with the costs of delayed discharge from excessive drowsiness or emesis. Decisions on drug use should not be limited to the costs of a drug but also should take into consideration the preferences of a patient. Our findings of an increased hospital stay and a decreased score in the parental assessment of the global perioperative experience in patients who vomited should be considered by the clinical anesthesiologist in a decision regarding the use of ondansetron in pediatric outpatient anesthesia.

In summary, this study demonstrated that ondansetron in a dose of 50 μg/kg was more effective than either a placebo or 10 μg/kg but not less effective than 100 μg/kg doses for the prophylaxis of postoperative emesis in the pediatric population.

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